Attorney Docket No.06472.0001-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,309,445

Issued: January 5, 1982

To: Richard J. Wurtman and Judith J. Wurtman

Assignee: Massachusetts Institute of Technology

Title of Patent: COMPOSITIONS UTILIZING d-FENFLURAMINE FOR MODIFYING FEEDING BEHAVIOR

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Your applicant, Interneuron Pharmaceuticals, Inc. ("Interneuron"), represents that it is the agent of the owner of record (the Massachusetts Institute of Technology or "MIT") of the entire interest in and to Letters Patent of the United States 4,309,445 granted to Richard J. Wurtman and Judith J. Wurtman on the 5th day of January, 1982 for COMPOSITIONS UTILIZING d-FENFLURAMINE FOR MODIFYING FEEDING BEHAVIOR. MIT is the owner of record by virtue of an assignment in favor of MIT recorded June 16, 1980, Reel 3776, Frame 323. Interneuron is MIT's authorized agent for the purposes of applying for and securing the patent term extension of U.S. patent 4,309,445 (Attachment A). By the Power of Attorney enclosed herein (Attachment B), Applicant appoints Charles E. Van Horn, Esq. of Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., as attorney for Interneuron

with regard to this application for extension of the term of U.S. Patent 4,309,445 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

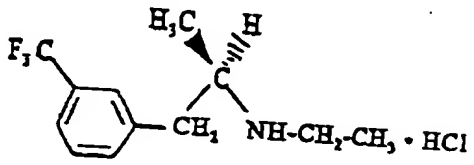
Applicant hereby submits this application for extension of patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. § 1.740). For the convenience of the Patent and Trademark Office, the information contained in this application will be presented in a format which will follow the requirements of 37 C.F.R. § 1.740.

1. **"A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics." 37 C.F.R. § 1.740(a)(1).**

The appropriate chemical and generic name for the approved product is dexfenfluramine hydrochloride, which is a novel pharmaceutical for treating the syndrome of carbohydrate craving during which the patient presents an abnormal appetite at definite hours of the day or night. By treating this syndrome, dexfenfluramine hydrochloride is useful in the treatment of obesity.

The approved product REDUX™[1/] (generic name "dexfenfluramine hydrochloride") has the:

(a) Structural Formula:



(b) Empirical Formula:

$C_{12}H_{16}NF_3 \cdot HCl$

(c) Molecular Weight:

267.7

(d) Chemical Name:

1. (S)-N-ethyl-∝-methyl-3-(trifluoromethyl) benzeneethanamine, hydrochloride
2. (+)-(S)-N-ethyl-∝-methyl-m-(trifluoromethyl) phenethylamine, hydrochloride

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1/ REDUX™ is the trademark of ORSEM (Servier).

3. (S)2-ethylamino 1-(3-trifluoromethyl phenyl) propane, hydrochloride
4. (S)-N-ethyl-1-[3-(trifluoromethyl)phenyl] propane-2-amine, hydrochloride
5. 1-(meta-trifluoromethylphenyl)-2-ethylaminopropane, hydrochloride

2. "A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred." 37 C.F.R. § 1.740(a)(2).

Section 505 of the Federal Food, Drug, and Cosmetic Act (FDC Act), 21 U.S.C. § 355, is the Federal statute under which the Food and Drug Administration's (FDA's) regulatory review of Interneuron's REDUX™ new drug application (NDA) for dexfenfluramine hydrochloride occurred. Section 505(b) of the FDC Act, 21 U.S.C. § 355(b), authorizes the filing of an NDA for a "new drug." FDA subsequently approved the REDUX™ NDA (NDA 20-344) under the authority granted the agency in Section 505(c) of the FDC Act, 21 U.S.C. § 355(c).

3. **"An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred." 37 C.F.R. § 1.740(a)(3).**

On April 29, 1996, FDA approved Interneuron's REDUX™ (dexfenfluramine hydrochloride) NDA under Section 505 of the FDC Act. Approval of the NDA authorizes the first commercial marketing of dexfenfluramine hydrochloride.

4. **"In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act." 37 C.F.R. § 1.740(a)(4).**

The active ingredient in REDUX™ is dexfenfluramine hydrochloride which has not been previously approved for commercial marketing or use under the FDC Act, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to the approval of the REDUX™ NDA on April 29, 1996.

We are aware that FDA has approved the racemate, fenfluramine, currently marketed in the U.S. by Wyeth-Ayerst,

under the trade name Pondimin®. (See Attachment E for additional information.)

5. **"A statement that the application is being submitted within the sixty day period permitted for submission pursuant to [37 C.F.R.] § 1.720(f) and an identification of the date of the last day on which the application could be submitted." 37 C.F.R. § 1.740(a)(5).**

This application is being submitted within the 60-day period following FDA approval of the REDUX™ NDA. FDA approved the REDUX™ NDA on April 29, 1996. This 60-day period for submission of this patent extension application will expire on June 28, 1996.

6. **"A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration." 37 C.F.R. § 1.740(a)(6).**

Interneuron is seeking an extension of U.S. Patent No. 4,309,445. The inventors are Richard J. Wurtman and Judith J. Wurtman. The date of issue for the patent is January 5, 1982, and the date of expiration is June 16, 2000, pursuant to 35 U.S.C. §§ 154(a) and 154(c)(1) (effective June 8,

1995 as a result of the enactment of Uruguay Round Agreements Act (URAA)).

7. **"A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings." 37 C.F.R. § 1.740(a)(7).**

A copy of the patent for which an extension is being sought is attached to this application (Attachment C). The patent contains two claims and no drawings.

8. **"A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent." 37 C.F.R. § 1.740(a)(8).**

There is no disclaimer, certificate of correction or reexamination certificate issued for U.S. Patent No. 4,309,445. The patent application for U.S. Patent No. 4,309,445 was filed on June 16, 1980 and, therefore, no maintenance fee payments are necessary under 35 U.S.C. § 41(b), which requires maintenance fees only for patents based on applications filed on or after December 12, 1980.

9. **"A statement that the patent claims the approved product or a method of using . . . the approved product, and a showing**

which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using. . .the approved product." 37 C.F.R. § 1.740(a)(9).

U.S. Patent No. 4,309,445 claims a condition of use which is included within the single approved indication for dexfenfluramine HCl. Dexfenfluramine HCl is a physiologically acceptable salt of 1-(meta-trifluoromethylphenyl)-2-ethylaminopropane. The patent claims are as follows:

1. A method for treating human patients having the syndrome of abnormal carbohydrate craving between meals which consists of administering to said patient a unit dosage form of a composition which comprises between about 5 mg and 100 mg per day of an active composition comprising the dextro optically active isomer of 1-(meta-trifluoromethylphenyl)-2-ethylaminopropane or a physiologically acceptable salt thereof in admixture with an inert non-toxic carrier.

2. A method of claim 1. wherein the dosage of the active isomer ranges from 10 to 60 mg per day.

The patent describes the syndrome of carbohydrate craving as "an abnormal appetite for carbohydrates at definite hours of the day or night."

The FDA approved labeling for dexfenfluramine HCl capsules – which will be marketed under the trade name REDUX™ – states that the drug "is indicated for the management of obesity including weight loss and maintenance in patients on a reduced calorie diet." The Clinical Pharmacology section of the FDA approved labeling includes a statement that in clinical studies, REDUX™ "was shown to preferentially decrease carbohydrate consumption at meals and to manage carbohydrate craving between meals by decreasing the consumption of snack foods with a high carbohydrate content in patients who frequently snack on such foods." The FDA approved labeling further states that treatment with REDUX™ "is associated with a reduction in appetite . . . [which] may contribute to the reduction in caloric consumption . . . ."

In terms of dosage, the FDA approved labeling states that the usual dosage is one 15 mg capsule twice daily, with meals. Dosages above 30 mg per day are not recommended. Therefore, both claims 1 and 2 cover the condition of use which is included within the single approved indication for REDUX™.

10. **"A statement . . . of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services . . . to determine the applicable regulatory review period . . . . For a patent claiming a human drug . . ., the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) . . . was initially submitted . . . and the date on which the NDA was approved . . . ." 37 C.F.R. §§ 1.740(a)(10), (i).**

In order to enable the Secretary to determine the applicable regulatory review period, the following information is provided:

(A) Interneuron filed its IND application for dexfenfluramine HCl (IND No. 38,108) on October 25, 1991 and it became effective on January 13, 1992.

(B) Interneuron's REDUX™ NDA (NDA No. 20-344) was initially submitted to FDA on May 23, 1993.

(C) The REDUX™ NDA (NDA No. 20-344) was approved by FDA on April 29, 1996.

11. **"A brief description . . . of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities." 37 C.F.R. § 1.740(a)(11).**

Attached is a chronology that briefly describes the significant regulatory activities and relevant dates associated with Interneuron's prosecution of this product before the FDA (Attachment D).

12. **"A statement . . . that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined." 37 C.F.R. § 1.740(a)(12).**

(i) It is the opinion of the applicant that U.S. Patent No. 4,309,445 is eligible for an extension. This opinion is based on the following information on U.S. Patent No. 4,309,445:

(a) 35 U.S.C. § 156(a) – U.S. Patent No. 4,309,445 claims a use of the approved human drug product dexfenfluramine hydrochloride, REDUX™.

(b) 35 U.S.C. § 156(a)(1) – The term of the patent has not expired prior to the submission of this application.

(c) 35 U.S.C. § 156(a)(2) – The term of said patent has never been previously extended under 35 U.S.C. § 156(e)(1). (A change in the patent expiration date was made only as a result of the patent term resetting provisions of the URAA set forth in § 154(c)(1) implementing the General Agreement on Tariffs and Trade (GATT).)

(d) This application for extension is in compliance with 37 C.F.R. § 1.740.

(e) 35 U.S.C. § 156(a)(4) – The product, REDUX™, has been subject to a regulatory review period as defined in 35 U.S.C. § 156(g) before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A) – The product received permission for commercial marketing or use on April 29, 1996 and this is the first permitted commercial marketing or use under the provision of law (i.e., FDC Act § 505) under which the applicable regulatory review occurred.

(g) The application has been submitted within 60 days from the April 29, 1996 approval date.

(h) 35 U.S.C. § 156(c)(4) – No other patent term has been extended for the same regulatory review period for this product.

(ii) It is the opinion of the applicant that U.S. Patent No. 4,309,445 is eligible for an extension of 1,322 days from June 16, 2000 to January 29, 2004. The length of this extension was determined as follows:

(A) The effective date of the IND application is January 13, 1992 and the IND number is 38,108.

(B) The NDA, No. 20-344, was initially submitted to the FDA on May 23, 1993.

(C) The NDA was approved by the FDA on April 29, 1996.

The following calculation of the regulatory review period is in accordance with 37 C.F.R. § 1.775:

A to B = 497 days (37 C.F.R. § 1.775(c)(1))

B to C = 1073 days (37 C.F.R. § 1.775(c)(2))

1073 + (497 x .5) = 1,322 days (37 C.F.R. § 1.775(d))

This extends the patent through January 29, 2004, which is the longest period allowed under Section 1.775 (d). This conclusion was reached as follows:

(a) Section 1.775(d)(4) requires the earlier date of either §§ 1.775(d)(2) and (d)(3):

(d)(2) = June 16, 2000 + 1,322 days = January 29, 2004

(d)(3) = April 29, 1996 + 14 years = April 29, 2010

(b) Section 1.775(d)(6)(ii)(B) further requires the earlier date of either (d)(4) or (d)(6)(i)(A):

(d)(4) = January 29, 2004

(d)(6)(i)(A) = June 16, 2000 + 5 years = June 16, 2005

13. "A statement that the applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services . . . any information which is material to the determination of entitlement to the extension sought." 37 C.F.R. § 1.740(a)(13).

The applicant hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of

Health and Human Services any information which is material to the determination of entitlement to the extension sought.

To this end, the applicant discloses that it is aware that FDA has taken a position, under Title I of the Drug Price Competition and Patent Term Restoration Act of 1984 ("Patent Term Restoration Act"), not entirely consistent with the applicant's assessment that a single specific enantiomer represents the "first permitted commercial marketing" of the product (that is, the "active ingredient") notwithstanding prior regulatory permission to market the undifferentiated racemate. (See Attachment E for additional discussion.)

14. "The prescribed fee for receiving and acting upon the application for extension." 37 C.F.R. § 1.740(a)(14).

In accordance with the fee schedule set out in 37 C.F.R. § 1.20(j), Interneuron encloses a check in the amount of $1,060.00. The Commissioner is authorized to charge any additional fees required by this application to Deposit Account No. 06-0916.

15. "The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for the patent term extension are to be directed." 37 C.F.R. § 1.740(a)(15).

Please direct all inquiries and correspondence relating to this application for patent term extension to:

Charles E. Van Horn, Esq.
Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

Tel: (202) 408-4000
Fax: (202) 408-4400

16. "A duplicate of the application papers certified as such." 37 C.F.R. § 1.740(a)(16).

Enclosed is a certification that this application for patent extension, including its attachments, is being submitted as one original and four (4) copies thereof (Attachment F).

17. "An oath or declaration [submitted in compliance with] paragraph (b) of this section." 37 C.F.R. § 1.740(a)(17).

The requisite declaration pursuant to 37 C.F.R. § 1.740(b) is attached (Attachment G).

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn
Charles E. Van Horn
Reg. No. 40,226

Dated: 25 June 1996

Attachments:

Interneuron as Agent of MIT (Attachment A)
Power of Attorney (Attachment B)
U.S. Patent No. 4,309,445 (Attachment C)
Chronology of Regulatory Review Period (Attachment D)
Supplemental Information (Attachment E)
Certification of Copies of Application Papers (Attachment F)
Declaration Pursuant to 37 C.F.R. § 1.740(b) (Attachment G)
Declaration to Complement the Declaration in Attachment G (Attachment H)

ATTACHMENT A

IPI is the authorized agent of MIT

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
28 Carleton Street, Room E32-300
Cambridge, MA 02142-1324

TECHNOLOGY LICENSING OFFICE

TELEPHONE (617) 253-6966
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TELEX 921473 MIT CAM

June 13, 1996

United States Patent and Trademark Office
Assistant Commissioner for Patents
Washington, D.C. 20231

Re: U. S. Patent 4,309,445

Dear Sirs:

This is to confirm that Interneuron Pharmaceuticals, Inc. is the authorized agent of the Massachusetts Institute of Technology for purposes of applying for and securing the patent term extension of U.S. patent 4,309,445 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Very truly yours,

Lita Nelsen

Lita L. Nelsen
Director

LLN:jbw

us.patent.ltr61396

ATTACHMENT B

Power of Attorney

Mark S. Butler
Executive Vice President
Chief Administrative Officer
and General Counsel

Interneuron Pharmaceuticals, Inc.
One Ledgemont Center
99 Hayden Avenue, Suite 340
Lexington, MA 02173
Tel: (617) 861-8444, Ext. 622
Fax: (617) 674-2448

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent 4,309,445
Issued:	January 5, 1982
To:	Richard J. Wurtman and Judith J. Wurtman
Assignee:	Massachusetts Institute of Technology
Title of Patent:	COMPOSITIONS UTILIZING d-FENFLURAMINE FOR MODIFYING FEEDING BEHAVIOR

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

POWER OF ATTORNEY

Interneuron Pharmaceuticals, Inc., as the authorized agent of the owner of the above-identified U.S. Letters Patent, hereby grants the power of attorney to **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER L.L.P., Reg. No. 22,540**, Charles E. Van Horn, Reg. No. 40,226; both jointly and separately to be its attorney with regard to an application for extension of the term of U.S. Patent 4,309,445 and to transact all business in the Patent and Trademark Office connected therewith.

Please send all future correspondence concerning the above matter to Charles E. Van Horn, Esq. at **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER L.L.P.**, at the following address:

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

INTERNEURON PHARMACEUTICALS, INC.

Date: June 14, 1996

Glenn L. Cooper, M.D.
President and Chief Executive Officer

Date: June 14, 1996

Mark S. Butler, Esq.
Executive Vice President, Chief Administrative Officer and General Counsel

ATTACHMENT C

Copy of Patent

United States Patent [19]

Wurtman et al.

[11] **4,309,445**

[45] **Jan. 5, 1982**

[54] **D-FENFLURAMINE FOR MODIFYING FEEDING BEHAVIOR**

[75] Inventors: **Richard J. Wurtman; Judith J. Wurtman, both of Boston, Mass.**

[73] Assignee: **Massachusetts Institute of Technology, Cambridge, Mass.**

[21] Appl. No.: **159,549**

[22] Filed: **Jun. 16, 1980**

[51] **Int. Cl.**[3] **A61K 31/13**

[52] **U.S. Cl.** **424/325**

[58] **Field of Search** 424/325

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,198,834 8/1965 Beregi et al. 260/570.8

OTHER PUBLICATIONS

Merck Index, 9th Ed. 1976, Entry No. 3902.
Wurtman et al., Science, vol. 198, pp. 1178–1180, 12/77.
Current Medical Research & Opinion, vol. 6, Suppl. 1, pp. 28–33, 1979.
Life Sciences, vol. 24, pp. 894–904, 1979.
Unger et al., Ann. Rev. Physiol., (1978), 40, p. 315.

Primary Examiner—Frank Cacciapaglia, Jr.
Attorney, Agent, or Firm—Arthur A. Smith, Jr.; Paul J. Cook

[57] **ABSTRACT**

Compositions containing controlled amounts of d-fenfluramine are administered to block the intermittent carbohydrate cravings without necessarily suppressing other food intakes.

2 Claims, No Drawings

D-FENFLURAMINE FOR MODIFYING FEEDING BEHAVIOR

BACKGROUND OF THE INVENTION

This invention concerns a new method of treating the syndrome of carbohydrate craving during which patients present an abnormal appetite for carbohydrate at definite hours.

At the present time, patients having a strong appetite for carbohydrate were not treated before appearance of obesity. At that stage, the use of compositions of large amounts of bulky substances or appetite-suppressant drugs have been utilized. The suppression of appetite was seen to result from a propensity to eat slower, to wait longer between meals, or to stop eating sooner. Such drugs show no selectivity on the kind of feeding and have unwanted side effects such as induction of hyperactivity.

A preferred method of treatment would involve the correction of the very nature of the feeding habits of some patients having an immoderate appetite for certain kinds of carbohydrate-containing food, particularly between meals. Such a state does not always entail obesity, but can indicate some metabolic disturbances or some neurotic troubles due to anxiety of becoming overweight.

Prior to the present invention, it has been known to administer dextro, levo-fenfluramine or fluoxetine to an animal (rat) in order to selectively reduce consumption of carbohydrates while not significantly reducing consumption of protein. These results are shown by Wurtman et al, *Science*, vol. 198, pp. 1178–1180, December, 1977; *Current Medical Research and Opinion*, vol. 6, Suppl. 1, pp. 28–33, 1979 and *Life Sciences*, vol. 24, pp. 894–904, 1979.

The d-isomer of fenfluramine and the salts thereof are known products which have been disclosed in the U.S. Pat. No. 3,198,834. In the same patent, the d-isomers at doses from about 5 mg to 50 mg per kg, have been generically disclosed as having an anorectic and a lipolytic activity in rates approximately three times greater than that of the corresponding l-isomer. The corresponding racemic mixture has an intermediate activity.

SUMMARY OF THE INVENTION

The present invention provides an appropriate treatment for carbohydrate cravings, i.e., for the patient presenting an abnormal appetite for carbohydrates at definite hours of the day or night. The invention is based on the discovery that the d-isomer of fenfluramine selectively eliminates this abnormal and intermittent appetite for carbohydrates while maintaining a normal protein and lipid intake. The effect of d-fenfluramine concerns all sweet foods and those which produce glucose during the gastrointestinal transit, and that such inhibition does not function simply through a control of the caloric intake.

DESCRIPTION OF SPECIFIC EMBODIMENTS

The present invention relates to novel pharmaceutical compositions for treating the syndrome of carbohydrate craving during which the patients present an abnormal appetite at definite hours of the day or night. Specifically, the invention provides pharmaceutical compositions having as an active ingredient the d-isomer of fenfluramine or 1-meta-trifluoro-methylphenyl-2-ethyl-aminopropane or a salt thereof mixed with an inert non-toxic pharmaceutical carrier.

Suitable additional salts can be formed from the following acids; the hydrohalic acid, sulfuric acid, phosphoric acid or an organic acid such as acetic acid, valeric acid, caproic acid, benzoic or nicotinic acid.

The inert non-toxic pharmaceutical excipient of choice utilized depends on the mode of administration. The compositions of this invention are suitable for parenteral, buccal, sublingual or rectal administration. The resulting pharmaceutical compositions are, for example, tablets, coated tablets, capsules, soft gelatine capsules, drinkable emulsions, suspensions or solutions for oral or injectable administration, sublingual tablets or suppositories. They may also be formulated into a sustained release form. Among the various excipients which may be used for these purposes include talc, magnesium stearate, calcium carbonate, sodium or magnesium phosphate, lactose or silica or the like. To the solid forms may be added a filler, a diluent, a binder such as ethyl-cellulose, dihydroxypropyl cellulose, carboxymethylcellulose, arabic gum, tragacanth gum or gelatine. The compositions of this invention may also be flavored, colored or coated with a wax or a plasticizer.

It has now been found that the d-isomer of fenfluramine is endowed with interesting and very specific properties which put it and its salts in a specific class among a broad disclosure of closely related compounds. This invention is based upon the discovery that the compositions of low doses of d-fenfluramine selectively suppress cravings for carbohydrates without disturbing the normal food intake.

We have found that such a special activity of the d-isomer which has never been suggested, is particularly useful for the treatment of patients having at definite hours of day or night a strong carbohydrate craving, that is an abnormal behavior of eating carbohydrate out of hunger.

Such patients are characterized by:

- a great appetite for carbohydrate foods which are often the same,
- an appetite often arising without anxiety,
- an appetite occurring according to a regular circadian cycle, and the resulting circadian maxima can be in relation to the menstruation cycle,
- often not overweight at the onset of the illness,
- sometimes associated with a so-called prediabetic state.

These patients need at definite hours, between meals, a high level of carbohydrate consumption in the form of snacks: doughnuts, fried potatoes, potato chips, pretzels, ice cream, whole meal or chocolate cookies, etc. Such a syndrome may be linked to signs of diabetus mellitus in persons at risk.

For these patients, the administration of a composition containing between about 5 to 200 mg of d-fenfluramine, depending upon the body weight of the patient, decreases the abnormal craving for carbohydrate foods at definite hours of the circadian cycle, and this result is not inhibited by the intake of a meal in which no visible alteration in the selection of basic nutrients has been observed. In accordance with this invention, d-fenfluramine is administered in an amount of between about 5 and 100 mg/day, preferably about 10 and 60 mg/day. At dosages above and below these amounts, the selective decrease of carbohydrate consumption does not occur to a significant degree.

The surprising and novel activity of the compositions of low doses of d-fenfluramine cannot be explained by the existing data on biological pharmacology of anorectic drugs which, at high doses, appear to depend on a different mechanism of action. The d-isomer of fenfluramine at usual or high dosage is more potent in inhibiting global food intake (protein and lipid as well as carbohydrate) than the l-isomer. This activity appears to be mediated by the serotoninergic system, since:

1. The neurochemical effects of those drugs on serotonin level in the brain are significantly modified and can explain how the global food intake is inhibited.

2. Other data show that lesions of the serotoninergic terminals in specific brain areas block the effect of high doses of dl-fenfluramine on global food intake.

3. The sedative action of these doses of dl-fenfluramine has also been considered as a consequence of serotoninergic mechanisms.

The new properties of compositions of low doses of d-fenfluramine which inhibit carbohydrate cravings, appear to depend on a different mechanism in relation to the central control of regulation of the energy balance: our observations show that its action is very similar to the action of somatostatin; a peptide localized in the hypothalamus, in the digestive endothelium and in the pancreatic islets. When injected into the 3rd ventricle of the rat, at very low doses, it decreases food intake and has a general behavioral effect of inhibition of the desire for carbohydrates, and inhibits absorption of carbohydrates. (Unger et al; Ann. Rev. Physiol, 1978, 40, p. 315).

While applicants do not intend to be bound by a theory of the mechanism of this invention, the following examples are merely intended to illustrate the invention and are not intended to limit the same.

EXAMPLE I

Selectivity in the Selection of Basic Nutrients at Low Doses

Material and Methods

Fifty-three male rats 21 to 48 days old (Charles River Breeding Laboratories, Wilmington, MA.) were housed singly in suspended cages and allowed free access to water. Room temperature was kept at 22° C. The animals were trained to consume all of their daily food during an 8-hour dark period and to select their food from two pans containing different diets which were isocaloric and contained 5 or 45 percent protein. The rats were injected with either d-fenfluramine (1.25 or 2.5 mg/kg), racemic fenfluramine (2.5 mg/kg) or saline at the beginning of the dark period and were given access to the food pans immediately afterwards. The pans were weighed before presentation and at intervals during the eight-hour feeding period. The number of grams of protein that each animal had consumed and the proportion of total caloric intake represented by this protein were calculated for each interval.

Results

TABLE I

EFFECT OF D-, AND DL-FENFLURAMINE UPON FOOD INTAKE AND PROTEIN CONSUMPTION

Number of Rats	Treatment	DIET 45% Protein	5% Protein	Total Food	Total Protein	% Protein
15	saline	5.2	3.1	8.4	2.5	29.7
12	1.25 mg/kg of d-fenflu.	4.5	1.0	5.5	2.1	37.8
7	2.5 mg/kg of d-fenflu.	2.8	2.0	4.8	1.36	28.3
19	2.5 mg/kg of dl-fenflu.	4.6	0.97	5.54	2.1	37.9

TABLE I-continued

EFFECT OF D-, AND DL-FENFLURAMINE UPON FOOD INTAKE AND PROTEIN CONSUMPTION

The superiority of d-fenfluramine is clearly shown because:

1. Both d- and dl-drugs reduced the total food intake, but the same result was obtained with half the dose of d-isomer.

2. At 1.25 mg of d-fenfluramine per kilo, rats reduced food intake but increased the proportion of protein from 29.7 to 37.8%, suggesting that a normal quantity of proteinic food was consumed, and that the quantity of carbohydrate was strongly decreased.

3. At 2.50 mg of d-fenfluramine per kilo, the selective anti-carbohydrate effect did not appear any more: this very particular figure of "inversion" of results with increasing doses is most familiar to physiologists and strongly suggests that a very specific system of regulation is concerned. It relates to a counter regulation mechanism overcoming the first at higher doses of the same drug. The whole history of research on autonomic nervous system drugs gives examples of such "diphasic" action, for very specific inhibitors.

4. The same specificity in protein intake was obtained with 2.50 mg/kg of the racemic mixture as well as with 1.25 mg/kg of the d-isomer, indicating that this effect was due only to d-fenfluramine, and that levo-fenfluramine has no significant effect. Accordingly, we found that higher doses of racemic mixtures (5 mg/kg) also had no selective effect on glucose food intake.

EXAMPLE II

Suppression of Consumption of Protein-Poor Diet by D-Fenfluramine

Materials & Methods

One hundred and twenty male rats, 21–48 days old, as above, received saline, dextro-levo fenfluramine (2.5 mg/kg), d-fenfluramine (1.25 or 2.5 mg/kg), or levo-fenfluramine (2.5 mg/kg) intraperitoneally, and were given access to food pans containing 5% or 45% protein (isocaloric; iso-carbohydrate) immediately thereafter. Data describe the grams of the protein-poor diet (5%) consumed during the subsequent one hour period.

Results

TABLE II

Treatment	Number of Rats	5% Protein Diet Consumed (Grams)
saline	46	3.48
dextro-levo fenfluramine (2.5)	41	1.01
d-fenfluramine (2.5)	10	1.54
d-fenfluramine (1.25)	12	0.30
levo fenfluramine (2.5)	11	3.70

As in Example I, d-fenfluramine administration caused a major decrease in the quantity of carbohydrate-rich, protein-poor food that the rats chose to consume. Half the d-l fenfluramine dose of 2.5 mg/kg was sufficient to

cause an even-more-major reduction in consumption of this diet, after d-fenfluramine; in contrast, 2.5 mg/kg of l-fenfluramine had no effect.

We claim:

1. A method for treating human patients having the syndrome of abnormal carbohydrate craving between meals which consists of administering to said patient a unit dosage form of a composition which comprises between about 5 mg and 100 mg per day of an active composition comprising the dextro optically active isomer of 1-(meta-trifluoromethylphenyl)-2-ethylaminopropane or a physiologically acceptable salt thereof in admixture with an inert non-toxic carrier.

2. A method of claim 1 wherein the dosage of the active isomer ranges from 10 to 60 mg per day.

* * * * *

ATTACHMENT D

Chronology of Significant Activities

ATTACHMENT D

CHRONOLOGY OF SIGNIFICANT ACTIVITIES AND DATES
REGARDING THE REDUX™ IND AND NDA

October 25, 1991	Original IND Submission (IND No. 38,108)
January 13, 1992	Effective date of IND
March 4, 1992	IND Information Amendment submitted to FDA
April 3, 1992	Clinical amendment
June 19, 1992	Clinical amendment, pharm/tox amendment
August 28, 1992	Clinical amendment
October 1, 1992	Clinical amendment, pharm/tox amendment, pK amendment
October 13, 1992	Clinical amendment, pharm/tox amendment
November 16, 1992	Toxicology final report submitted to FDA, pharm/tox amendment
February 1, 1993	IND Annual Report submitted to FDA.
May 21, 1993	FDA indicates that Dexfenfluramine NDA may be transferred to Metabolic and Endocrinologic Division.
May 23, 1993	REDUX™ NDA (NDA No. 20-344) is submitted to the FDA.
May 24, 1993	NDA received by Neuropharmacologic Division.
June 1, 1993	NDA officially transferred from Neuropharmacologic Div. to Metabolic and Endocrinologic Div. along with all other anti-obesity compounds.
July 24, 1993	NDA is officially filed at the FDA.
August 9, 1993	FDA confirms NDA was filed.
August 19, 1993	Compliance Division asks for specific study files and CRF's.
August 20, 1993	FDA field office inquires about pre-approval inspection.
August 27, 1993	Notification given to FDA of clinical studies which have been completed and final reports generated.
September 20, 1993	Division of Biometrics requests carcinogenicity data sets (IPI responded September 22, 1993).

October 5, 1993	IPI met with FDA to demonstrate CANDA.
October 13, 1993	Division of Biometrics requests clinical study efficacy datasets (IPI responded October 15, 1993).
October 15, 1993	Presented CANDA prototype to FDA.
October 19, 1993	Division of Biometrics requests clinical study efficacy datasets (IPI responded October 22, 1993).
October 27, 1993	120-day Safety Update submitted.
November 23, 1993	FDA requests extension (90 days) to complete NDA review (chemistry, pharmacology and toxicology review complete).
November 30, 1993	IPI delivers CANDA.
December 20, 1993	Reviewing chemist asks an additional question.
January 7, 1994	FDA requests copy of a non-IND Protocol (IPI responded January 7, 1994).
January 11, 1994	Clinical amendment
January 31, 1994	IND Annual Report
January 31, 1994	FDA district office requests copy of CMC section of NDA.
January 31, 1994	FDA sends questions regarding several pharmacokinetic studies (IPI responded February 10, 1994).
February 10, 1994	Respond to FDA's request for method validations for biopharm studies.
February 16, 1994	Pharm/tox amendment
February 16, 1994	Pharm/tox amendment
February 17, 1994	Clinical biopharm amendment
February 22-24, 1994	Manufacturing facility pre-approval inspection
February 23, 1994	Other amendment – Literature
March 4, 1994	Other Amendment – Bibliographies
March 7, 1994	CMC Amendment, response to Dr. Hillman.
March 15, 1994	Clinical/other amendment
March 28, 1994	Pharm/tox amendment
April 11, 1994	Meeting with FDA

April 12, 1994	Clinical/other amendment
April 19, 1994	FDA Div. of Biometrics requests clinical study database (submitted April 27, 1994).
April 28, 1994	Pharm/tox amendment
May 3, 1994	Submitted Major CMC Amendment
May 23, 1994	Clinical amendment
June 6-10, 1994	Manufacturing facility pre-approval inspection by FDA.
August 9, 1994	IPI submitted additional clinical analysis.
September 6, 1994	Clinical amendment
September 14, 1994	IPI submitted updated literature search, revised French labeling, neurochem report, Tables A-D and CMC information.
September 29,30 - October 3, 1994	FDA inspects manufacturing facility.
December 2, 1994	Clinical amendment
December 6, 1994	Clinical amendment
December 12, 1994	Other amendment, CMC amendment
January 10-12, 1995	FDA inspection of manufacturing facility.
February 6, 1995	Other amendments
February 17, 1995	IPI receives "non-approvable" letter.
February 24, 1995	Interneuron filed response to non-approvable letter (intent to respond) under 21 C.F.R. § 314.120(a)(1).
March 10, 1995	IND Annual Report submitted to FDA.
May 12, 1995	Interneuron responds to "non-approvable" letter.
May 26, 1995	Other amendment
June 30, 1995	Interneuron submits patent term extension per GATT rulings.
July 25, 1995	Meeting with FDA
August 22, 1995	pK amendment, pharm/tox amendment
September 5, 1995	Clinical amendment
September 28, 1995	Metabolic and Endocrinologic Advisory Committee Meeting.

September 29, 1995	Drug Abuse Advisory Committee meeting (joint meeting with Metabolic and Endocrinologic Advisory Committee).
October 16, 1995	Pharm/tox amendment
October 18, 1995	Clinical amendment
November 1, 1995	Clinical amendment, pharm/tox amendment
November 10, 1995	Pharm/tox amendment
November 16, 1995	Metabolic and Endocrinologic Advisory Committee Meeting.
December 6, 1995	Clinical amendment
December 11, 1995	pK amendment, clinical amendment
January 31, 1996	Clinical amendment
February 5, 1996	Draft labeling amendment
February 14, 1996	Clinical amendment
February 15, 1996	Draft labeling amendment
March 7, 1996	Draft labeling amendment
March 12, 1996	Interneuron submits annual IND report.
March 29, 1996	Draft labeling amendment
April 3, 1996	Clinical amendment
April 29, 1996	REDUX™ NDA (NDA 20-344) approved by FDA.

ATTACHMENT E

Supplemental Information

Supplemental Information

The statutory standard for patent term extension is that, among other things, the NDA for dexfenfluramine hydrochloride constitutes "the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred." 35 C.F.R. § 156(a)(1)(A). Dexfenfluramine hydrochloride is a "drug product," which is defined as "the active ingredient . . . including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient." 35 U.S.C. § 156(f)(2).

Dexfenfluramine hydrochloride is the dextrorotary enantiomer of racemic fenfluramine. Racemic fenfluramine is the subject of an NDA approved by FDA in 1973.

In the preamble to FDA's 1989 proposed regulations implementing the marketing exclusivity provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 ("Patent Term Restoration Act"), FDA stated that in determining whether a product is entitled to five years of marketing exclusivity, the agency will "consider whether a drug contains a previously approved active moiety on a case-by-case basis." 54 Fed. Reg. 28898 (July 10, 1989). FDA also stated in the preamble that a "single enantiomer of a previously approved racemate

contains a previously approved active moiety and is therefore not considered a new chemical entity." Id. This conclusion was reiterated in the preamble to the 1994 final rule. 59 Fed. Reg. 50359 (Oct. 3, 1994).

Accordingly, it is possible that FDA, if queried by the Patent and Trademark Office as to the eligibility of the dexfenfluramine hydrochloride patent subject to this extension request, may state the view that the NDA for dexfenfluramine hydrochloride is not the "first permitted commercial marketing or use" of that enantiomer by reason of the prior approval of the NDA for racemic fenfluramine.

For the following reasons, we disagree with that hypothetical position.[1/]

I. FDA's Exclusivity Rule Does Not Govern Interpretation Of The Eligibility Criteria For Patent Term Extension

FDA's hypothetical position would necessarily be based on its interpretation of the 5-year exclusivity provision of the Federal Food, Drug, and Cosmetic Act (FDC Act). 21 U.S.C. § 355(j)(4)(D)(ii). FDA's interpretation is that Congress intended to grant 5-year exclusivity only to "new chemical entities," which FDA defines as "active moieties" that have not

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1/ FDA has never taken the position that a racemate consists of the enantiomers "in combination." Therefore, we do not address that point in this explanation.

been "approved in" any previous NDA. As explained below, we do not believe that dexfenfluramine was "approved in" the NDA for fenfluramine so as to disqualify it for 5-year exclusivity under the FDC Act. But even if that were the case, the disqualification would result from FDA's interpretation of the FDC Act.

The PTO must apply the terms of the patent law, not the FDC Act. Although the definition of "drug product" in 35 U.S.C. § 156(f)(2) contains language similar to that in the eligibility criterion for 5-year exclusivity, the definition is not identical.[2/] More important, it is part of a separate statutory scheme, with its own structure, legislative history, and judicial precedents.[3/]

2/ Title I of the Act grants five years of marketing exclusivity to "an application submitted under subsection (b) [21 U.S.C. § 355(b)] for a drug, no active ingredient (including an ester or salt of the active ingredient) of which has been approved in any other application under subsection (b)." 21 U.S.C. §§ 355(c)(3)(D)(ii) and (j)(4)(D)(ii).

3/ The 1984 Act had two general purposes: (1) to increase the availability of low-cost drugs by expanding a generic drug approval procedure; and (2) to further encourage new drug research by restoring some of the patent term lost while drug products undergo testing and await FDA premarket approval Glaxo Operations UK Ltd. v. Quigg, 894 F.2d 392, 396, 13 U.S.P.Q. 2d 1628, 1631 (Fed. Cir. 1990). Title II of the Act, now codified in 35 U.S.C. § 156, contains the requirements, procedures and definitions applicable to patent term extension. Congress specifically authorized the Commissioner to make a determination that a patent is eligible for extension solely on the basis of the representations contained in the application for the extension (Section 156(e)(1)). The patent term extension provisions also are distinct from the drug exclusivity part of that 1984 law in that Congress further provided that

(continued...)

In the statutory scheme established for deciding questions of patent term extension, the only relevant question is whether "the active ingredient" of dexfenfluramine, "including any salt or ester of the active ingredient," was the subject of a "permitted commercial marketing or use" as the result of FDA's approval of an NDA for fenfluramine. The answer to this question is that it was not.

First, the "active ingredient" of dexfenfluramine is the dextrorotary enantiomer of fenfluramine. The NDA for racemic fenfluramine did not "permit" the commercial marketing or use of dexfenfluramine under the FDC Act.

Second, the legislative history of the Patent Term Restoration Act makes clear that the only FDA approval that matters in deciding whether a patent is entitled to extension is the approval of the specific product – active ingredient – to which the patent applies:

> [T]he approved product must have been approved for commercial marketing for the first time.

H.R. Rep. No. 857, 98th Cong., 2d Sess., Part 1, at 14-15, reprinted in 1984 U.S.C.C.A.N. 2647, 2648 (emphasis added).

3/ (...continued)
invalidity of the extension of the patent term under Section 156(e)(1) shall be a defense in any action involving the infringement of a patent during the period of the extension of its term (Section 282).

Third, the Federal Circuit has made clear that the "plain meaning" of the patent term extension statute requires that a patent be found eligible for extension if the "active ingredient" of the "product" subject to the regulatory review period was not previously approved by FDA. Glaxo Operations UK Ltd. v. Quigg, 894 F.2d 392, 395 (Fed. Cir. 1990). The court specifically stated that the PTO has no discretion to determine what "product" means, id. at 399, and that "active ingredient" has a "well-defined, ordinary, common meaning[]." Id. at 395.

The "active ingredient" in the "drug product" dexfenfluramine is the dextrorotary enantiomer. There is no question that the NDA for dexfenfluramine approved on April 29, 1996, was the first approval by FDA of the dextrorotary enantiomer for commercial sale. Accordingly, the NDA was the "first permitted commercial marketing or use" of dexfenfluramine. Therefore, under the plain meaning of the statute, consistent with the legislative history, and in line with the Federal Circuit view, the dexfenfluramine patent is eligible for extension.

II. FDA's Interpretation Is Inconsistent With The FDC Act

A. The Physical Presence of the Dexfenfluramine Enantiomer "in" the Fenfluramine Racemate Did Not Result in the Enantiomer Being "Approved" in the NDA for the Racemate

Dexfenfluramine hydrochloride is the dextrorotary enantiomer of the racemate fenfluramine. Under the trade name Pondimin®,

fenfluramine currently is marketed in the United States by Wyeth-Ayerst. It is the subject of NDA-16-618, which was approved by the FDA in 1973 for the treatment of exogenous obesity, as an adjunct to a weight reducing diet.

FDA did not "approve" the "active ingredient"[4/] of dexfenfluramine hydrochloride in the NDA for Pondimin®. The active ingredient in a racemate that is "approved" in an NDA is the undifferentiated racemate, not the isolated enantiomers individually. The only safety and effectiveness data required and evaluated in the NDA for fenfluramine were derived from studies in which the racemate as such was administered. Such studies yielded no data about the enantiomers as distinct entities, as FDA itself recognized by requiring full safety and effectiveness testing when the single enantiomer, dexfenfluramine, was later offered for approval as a separate active ingredient.

In summary, while the dextrorotary enantiomer, dexfenfluramine, may be "in" the approved racemate, fenfluramine, the enantiomer was not an "active ingredient . . . approved in"

4/ FDA interprets "active ingredient" in the FDC Act exclusivity provisions as synonymous with "active moiety." For purposes of this explanation of Interneuron's position, it is unnecessary to address the question whether FDA's interpretation is appropriate under the FDC Act. The question is not whether dexfenfluramine is an "active moiety." The question is whether dexfenfluramine was "approved in" the NDA for fenfluramine, irrespective of whether it is characterized as an "active ingredient" or an "active moiety."

the fenfluramine NDA.[5/] Accordingly, the NDA for dexfenfluramine is the "first permitted commercial marketing or use of the product" consisting of dexfenfluramine, and the dexfenfluramine patent is thus eligible for a patent term extension under the Patent Term Restoration Act.

B. The Studies That FDA Required Of Dexfenfluramine Hydrochloride Prior To Approval Of The Redux NDA Underscore That The Agency Did Not View The Product As Having Been Previously Approved

The NDA for the fenfluramine racemate did not include the information that would have been necessary for dexfenfluramine hydrochloride to have been "approved in" the fenfluramine NDA. The information in the fenfluramine NDA consisted only of observations about and measurements of the effects of the racemate. The safety and effectiveness conclusions FDA drew from those observations and measurements applied only to the racemate. The information in the fenfluramine NDA was incapable of supporting safety and effectiveness conclusions sufficient to allow approval of an NDA for the dextrorotary enantiomer,

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5/ To generalize: The enantiomers of <u>any</u> racemate are likely to have different properties. For instance, a racemate approved as a "drug" may include an enantiomer with useful pharmacological properties and an enantiomer that is a distomer or that has pharmacological activities that are not relevant to the indication for which the racemate is approved. Self-evidently, the mere presence of the undesirable or irrelevant enantiomer "in" the racemate does not mean that such enantiomer as a separate entity was "approved in" the NDA for the racemate. It follows that the pharmacologically useful enantiomer is also not "approved in" the NDA for the racemate simply because it was physically "in" the racemate. The only substance "approved in" an NDA for a racemate is the racemate as such.

dexfenfluramine hydrochloride. In fact, in the FDA approved labeling for the fenfluramine racemate, there is no identification of the isomers that are part of the racemate, and no reference to safety or efficacy information on the dextrorotary, or any other, isomer of the racemate. Therefore, the NDA for the fenfluramine racemate only examined the undifferentiated racemate in the aggregate, without any evidence that particular isomers of fenfluramine had any pharmacologic activity by themselves, were inert, were toxic, or were safe and effective.

Consequently, in reviewing Interneuron's NDA for the dextrorotary enantiomer by itself, FDA treated the enantiomer as a new chemical entity, separate and distinct from its racemate. FDA thus required submission of a quantum of data for dexfenfluramine's approval comparable to that required for any other new chemical entity. At a meeting in April 1991 to plan for the eventual submission of an NDA for dexfenfluramine, officials in the FDA Division of Neuropharmacological Drug Products explained that it was the position of the Division that FDA should treat dexfenfluramine as a new drug product based, in part, on the reports in the literature indicating that

dexfenfluramine and the levorotary enantiomer, L-fenfluramine, have "different pharmacological and toxicological properties."[6/]

Because FDA required Interneuron to submit in support of its dexfenfluramine hydrochloride NDA a quantity and type of data comparable to those required for a new chemical entity, then as a matter of statutory interpretation and scientific logic, the drug was one whose active ingredient was not "approved in" another NDA, i.e., the racemate fenfluramine's NDA. If dexfenfluramine had been "approved in" the fenfluramine NDA, FDA would not have required the submission of an entirely independent and complete

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6/ Officials in the Division also indicated that information such as, but not limited to, the following would be required for FDA approval of dexfenfluramine:

- A one year chronic dosing study.
- Reproduction/teratology studies.
- Two-year carcinogenicity studies in the rat and the mouse.
- Additional information on the prolonged neurochemical changes associated with dexfenfluramine.
- A standard battery of biopharmaceutic studies including single dose pharmacokinetics (PK), multiple dose PK, food effect, diurnal variation, dose proportionality, protein binding, and radiolabeled ADME.
- In the biopharmaceutic studies, FDA officials indicated that both enantiomers of the parent drug and their metabolites would have to be measured in biological samples in each of the studies.
- Clinical pharmacology and controlled clinical studies.
- The adverse experience reports for dexfenfluramine for the first six months following market introduction in the United Kingdom.

data set showing that the dextrorotary enantiomer, by itself, was safe and effective.

Accordingly, the NDA for dexfenfluramine was the "first permitted commercial marketing or use" of the product consisting of the single dextrorotary enantiomer as the active ingredient, as opposed to the undifferentiated racemate. The patent for dexfenfluramine is therefore eligible for extension. The legislative history of the Patent Term Restoration Act supports this conclusion.

> The purpose . . . of the bill is to create a new incentive for increased expenditures for research and development of certain products which are subject to premarket government approval. The incentive is the restoration of some of the time lost on patent life while the product is awaiting pre-market approval. Under current law, a patent continues to run while the maker of the product is testing and awaiting approval to market it.

H.R. Rep. No. 857, 98th Cong., 2d Sess., Part 1, at 14-15, reprinted in 1984 U.S. Code Cong. & Admin. News 2647, 2648. The "incentive" was intended to encourage research and development of products where the "first approval for commercial marketing or use of that product" is delayed by regulatory review. Id. at 2706 (emphasis added). "The product" to which this incentive applies is thus the specific product for which FDA required extensive testing of the type necessary for approval of an original NDA, which aptly describes the NDA FDA required Interneuron to submit for dexfenfluramine.

C. FDA And Court Precedent Further Support The Conclusion That Dexfenfluramine Hydrochloride Will Be The First Permitted Commercial Marketing Of The Product

FDA's granting of five years of marketing exclusivity for Oclassen Pharmaceutical's Condylox (podofilox) 0.5% solution under the exclusivity sections in the FDC Act, sections 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii), further supports the conclusion that the NDA for dexfenfluramine hydrochloride is the first permitted commercial marketing of the product and therefore that the patent for dexfenfluramine is eligible for patent term extension under the Patent Term Restoration Act.[7/]

The NDA for podofilox to treat genital warts was approved in 1990. Podofilox can be derived from podophyllum and podophyllum resin (also called podophyllin), both of which were ingredients in drugs subject to pre-1962 NDAs for the same indication. Apparently, FDA was uncertain whether podofilox should be granted five years of exclusivity under sections 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the FDC Act. The most likely explanation for the agency's equivocation was that FDA believed five years of exclusivity might be inappropriate because podofilox was a constituent of the ingredient in the drugs subject to the previously approved NDAs. Nonetheless, in a July 21, 1993

7/ There are other FDA precedents on the similar topic of the 5-year period of so-called Waxman-Hatch exclusivity as well as PTO precedents on patent extension (e.g., Promit). This section only presents one illustration of the precedents in this area and should not be viewed as an exhaustive treatment.

letter, an agency official notified Oclassen's attorneys that the Condylox NDA would be granted five years of exclusivity:

> After careful consideration, we agree that the approval of NDA 19-795 represented the first approval of podofilox under section 505(b) of the Act. Although, as you acknowledge, several previously approved NDAs contained podophyllum or podophyllum resin, the agency has determined that these previously approved NDA's did not characterize podofilox as an active ingredient. Consequently, your request for five-year exclusivity for podofilox is granted. . . .

The logic of FDA's decision to grant Oclassen five years of exclusivity because it was the first "active ingredient" of its kind approved by FDA applies equally to the dextrorotary enantiomer of the fenfluramine racemate. Essentially podofilox was "in" the active ingredient of the products subject to a previously approved NDAs, but was not the active ingredient "approved in" the NDAs for those products: the previously approved NDA did not include any safety and efficacy information on the specific podofilox moiety, nor did FDA require any such information for that prior approval. The same is true of the dextrorotary enantiomer of the approved fenfluramine racemate.[8/]

Court decisions also support the interpretation that FDA approval of a racemate does not constitute approval of the enantiomers in the racemate. For example, in Abbott Laboratories v. Young, 920 F.2d 984 (D.C. Cir. 1990), cert. denied sub nom. Abbott Laboratories v. Kessler, 112 S. Ct. 76 (1991), which

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8/ There is no patent for the podofilox product listed in FDA's Orange Book. Consequently, this FDA precedent does not have a patent extension counterpart.

involved the ten-year exclusivity provision of the 1984 law, 21 U.S.C. § 355(j)(4)(D)(i), the court recognized that Congress's decision to specify salt and ester variations as ineligible for ten or five years of exclusivity precludes FDA from disqualifying other drugs on the theory that a chemically related drug was tested and approved in a prior NDA. According to the court:

> We cannot agree with the government's unconvincing attempts to employ the "including" clause to cover all possible permutations of active ingredient. . . . It is simply not plausible to read "including any salt or ester" as merely illustrative, to mean including any form that eventually produces the same active moiety.

920 F.2d at 988.

In Glaxo Operations UK Ltd. v. Quigg, 894 F.2d 392, 395 (Fed. Cir. 1990), the court similarly found the "ester and salt" language of 35 U.S.C. § 156 to have a "plain meaning" that permitted no administrative interpretation. The dextrorotary enantiomer of the racemate fenfluramine is not a "salt or ester" of the racemate fenfluramine. Nor was the enantiomer "approved in" the NDA for the racemate. Accordingly, the NDA for dexfenfluramine is "the first permitted commercial marketing or use" of the product consisting solely of the dextrorotary enantiomer of fenfluramine.

ATTACHMENT F

Submission Certification

Attorney Docket No. 6472.0001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,309,445

Issued: January 5, 1982

To: Richard J. Wurtman and Judith J. Wurtman

Assignee: Massachusetts Institute of Technology

Title of Patent: COMPOSITIONS UTILIZING d-FENFLURAMINE FOR MODIFYING FEEDING BEHAVIOR

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

CERTIFICATION

I, CHARLES E. VAN HORN, do hereby certify that this accompanying application for extension of the term of U.S. Patent 4,309,445 under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and four (4) copies thereof.

Respectfully submitted,

Charles E. Van Horn

Charles E. Van Horn
Reg. No. 40,266

Date: 25 June 1996

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

ATTACHMENT G

Patent Extension Certification

Attorney Docket No. 6472.0001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,309,445

Issued: January 5, 1982

To: Richard J. Wurtman and Judith J. Wurtman

Assignee: Massachusetts Institute of Technology

Title of Patent: COMPOSITIONS UTILIZING d-FENFLURAMINE FOR MODIFYING FEEDING BEHAVIOR

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION ACCOMPANYING APPLICATION UNDER 35 U.S.C. § 156 FOR EXTENSION OF PATENT TERM

I, CHARLES E. VAN HORN, do hereby declare:

I am a patent attorney authorized to practice before the United States Patent and Trademark Office and I have been appointed as an attorney by Interneuron Pharmaceuticals Inc., the authorized agent to the owner of record of this patent, with regard to this application for extension of the term of U.S. Patent 4,309,445 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

I have reviewed and understand the contents of the accompanying application being submitted pursuant to 37 C.F.R. § 1.740.

I believe that the patent qualifies for and is subject to extension pursuant to 35 U.S.C. § 156 and 37 C.F.R. § 1.710.

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

I believe that an extension of the length claimed is justified under 35 U.S.C. § 156 and applicable regulations.

I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Charles E. Van Horn

Charles E. Van Horn
Reg. No. 40,266

Date: 25 June 1996

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202-408-4000

ATTACHMENT H

Supplemental Patent Extension Certification

Attorney Docket No. 06472.0001-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,309,445

Issued: January 5, 1982

To: Richard J. Wurtman and Judith J. Wurtman

Assignee: Massachusetts Institute of Technology

Title of Patent: COMPOSITIONS UTILIZING d-FENFLURAMINE FOR MODIFYING FEEDING BEHAVIOR

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION TO COMPLEMENT ATTACHMENT G

I, FRANK J. SASINOWSKI, do hereby declare:

I am regulatory counsel to Interneuron Pharmaceuticals, Inc. and have been since the formation of that company.

For the first three years after enactment of 35 U.S.C. § 156 as part of the Drug Price Competition and Patent Term Restoration Act of 1984, I was the FDA official charged with the primary responsibility for organizing the execution of FDA's responsibilities under 35 U.S.C. § 156. Among other issues, this meant developing the policies, procedures and precedents for providing the U.S. Patent and Trademark Office with assistance in determining whether an FDA approved product represented the "first permitted commercial marketing" of that product. (For the

FDA regulation that spells out this FDA function, see 21 C.F.R. § 60.10. A copy is attached.)

As Mr. Charles Van Horn has affirmed in his certification (Attachment G), I too have reviewed this patent extension application and, based on my knowledge of and experience with such eligibility determinations, concur with Mr. Van Horn's assessment that this patent is eligible for extension under 35 U.S.C. § 156.

Respectfully submitted,

Frank J. Sasinowski, Esq.

Dated: June 25, 1996

code of federal regulations

Food and Drugs

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PARTS 1 TO 99

Revised as of April 1, 1995

CONTAINING
A CODIFICATION OF DOCUMENTS
OF GENERAL APPLICABILITY
AND FUTURE EFFECT

AS OF APRIL 1, 1995

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as a Special Edition of
the Federal Register

Subpart B—Eligibility Assistance

§ 60.10 FDA assistance on eligibility.

(a) Upon written request from the U.S. Patent and Trademark Office, FDA will assist the U.S. Patent and Trademark Office in determining whether a patent related to a product is eligible for patent term restoration as follows:

(1) Verifying whether the product was subject to a regulatory review period before its commercial marketing or use;

(2) For human drug products, food additives, color additives, and medical devices, determining whether the permission for commercial marketing or use of the product after the regulatory review period is the first permitted commercial marketing or use of the product either:

(i) Under the provision of law under which the regulatory review period occurred; or

(ii) Under the process claimed in the patent when the patent claims a method of manufacturing the product that primarily uses recombinant deoxyribonucleic acid (DNA) technology in the manufacture of the product;

(3) For animal drug products, determining whether the permission for commercial marketing or use of the product after the regulatory review period:

(i) Is the first permitted commercial marketing or use of the product; or

(ii) Is the first permitted commercial marketing or use of the product for administration to a food-producing animal, whichever is applicable, under the provision of law under which the regulatory review period occurred;

(4) Informing the U.S. Patent and Trademark Office whether the patent term restoration application was submitted within 60 days after the product was approved for marketing or use, or, if the product is an animal drug approved for use in a food-producing animal, verifying whether the application was filed within 60 days of the first approval for marketing or use in a food-producing animal; and

(5) Providing the U.S. Patent and Trademark Office with any other information relevant to the U.S. Patent and Trademark Office's determination of whether a patent related to a product is eligible for patent term restoration.

(b) FDA will notify the U.S. Patent and Trademark Office of its findings in writing, send a copy of this notification to the applicant, and file a copy of the notification in the docket established for the application in FDA's Dockets Management Branch (HFA-305), rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

[57 FR 56261, Nov. 27, 1992]